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Systemic and airway inflammation and the presence of emphysema in patients with COPD

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Summary
The aim of this study was to determine the impact of HRCT-confirmed emphysema on biomarkers evaluating airway and systemic inflammation in COPD patients.

Forty-nine consecutive male COPD outpatients with stable COPD were divided in two groups according to the presence or absence of emphysema on HRCT. Patients underwent pulmonary function tests, plus assessment of exercise capacity, body composition and quality of life. Biomarkers were measured in serum (CRP, interleukin-6, TNF-α, leptin, adiponectin, osteocalcin, insulin growth factor-1, and systemic oxidative stress), in plasma (fibrinogen and VEGF) and in whole blood (B-type natriuretic peptide). TNF-α, 8-isoprostane and pH were additionally measured in exhaled breath condensate.

Patients with emphysema had more severe lung function impairment, lower body-mass index and fat-free mass index, and poorer quality of life. Additionally, they presented increased systemic oxidative stress and plasma fibrinogen and lower BNP compared to patients without emphysema. After proper adjustment for disease severity, all differences remained with the exceptions of body-mass index, fat-free mass index and BNP.

COPD patients with HRCT-confirmed emphysema present increased systemic oxidative stress and fibrinogen, suggesting that they may be more prone to the systemic consequences of COPD compared to patients without emphysema.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible, usually progressive, and associated with an abnormal inflammatory response of the lungs in response to noxious particles and gases.[1] COPD is associated with both airway and systemic inflammation.[2] Airway inflammatory markers are higher in more severe disease and increase during COPD exacerbations.[2] There is evidence that systemic inflammation is present even in stable COPD and the intensity of the inflammatory process may be related to the severity of the underlying disease.[3] Recently it has been suggested that COPD might be a part of a chronic systemic inflammatory syndrome.[4] Several systemic inflammatory markers, such as C-reactive protein (CRP) and fibrinogen, are increased in patients with COPD both in stable disease and in exacerbations.[2,5–7]

The two major subtypes, chronic bronchitis and emphysema, lead in the two clearly distinguishable phenotypes of the ''blue bloater'' and the ''pink puffer''. Despite the fact that emphysema can occur in both phenotypes, it is more frequently observed in the ''pink puffer'' phenotype.[8] The introduction of high resolution computed tomography (HRCT) has brought a new dimension to the study of COPD, as it offers the opportunity to study the pathologic processes involved in structural changes within the lung and to investigate the severity, extension and distribution of emphysema.[9,10] Besides the well-studied aforementioned features of the two phenotypes, recent studies have evaluated differences between patients with and without emphysema on HRCT, reporting that COPD patients with HRCT-confirmed emphysema are characterized by more severe lung function impairment, more intense airway inflammation as evaluated by induced sputum, and possibly more serious systemic dysfunction.[11] However, possible differences in biomarkers of airway and systemic inflammation have not been fully evaluated in relation to the presence of emphysema.

The aim of the present study was to determine the impact of the presence of HRCT-confirmed emphysema on biomarkers that have been previously used to evaluate airway and systemic inflammation in patients with COPD. Health-related quality of life, body composition, and lung function were additionally assessed in patients with and without emphysema, and correlations with local and systemic inflammatory biomarkers were evaluated.

Materials and methods

Subjects

Detailed methodology is provided in the Supplementary material. We enrolled 49 consecutive male outpatients with stable COPD. Patients with significant comorbidities, including cardiovascular disease, were meticulously excluded. No patient was receiving any form of corticosteroids 4 weeks prior to samples collection. The study protocol was approved by the local ethics committee and patients provided written informed consent.

Study design

Exhaled breath condensate (EBC) was collected using a commercial condenser (EcoScreen, Viasys, Germany).[12] Blood was centrifuged at 1500 *g* for 15 min at 4 °C and samples were stored at −80 °C. Arterial blood gases were measured using a commercial analyser (Instrumentation Laboratories, Milan, Italy). Patients were subsequently submitted to: (a) Pulmonary function tests with a commercially available system (Master Screen, Erich Jaeger GmbH, Wuerzburg, Germany).[13] (b) Assessment of body composition with Bioelectrical Impedance Analysis (BIA 101 System Analyser, Akern, Florence, Italy)[14,15]; body mass index (BMI) was calculated as weight/height squared and fat-free mass index (FFMI) was calculated as FFM/height squared.[16] (c) Evaluation of exercise capacity with the 6-minute walk test.[17] (d) Chest high resolution computed tomography (HRCT) using either a Somaton HiQ or a Somaton Plus scanner (Siemens, Erlanger, Germany). The degree of emphysema was calculated using a visual emphysema score as previously described.[18] The presence of emphysematous lesions involving $\geq$15% of the pulmonary parenchyma were used for the characterization of the emphysematous phenotype, as previously described in COPD.[11] Dyspnea was assessed with the modified Medical Research Council (MRC) scale[19] and BODE index was determined.[20] HRQoL was assessed with Saint George's Respiratory Questionnaire.[21] Patients were additionally submitted to echocardiography by an experienced cardiologist (E.Z.) to exclude cardiovascular comorbidities.

Measurements of biomarkers

Serum CRP and plasma fibrinogen were quantified by immunonephelometry (Behring Nephelometer Analyzer-II). Serum IL-6 and TNF-α and plasma VEGF levels were measured using commercial ELISA kits (Biosource Europe, Nivelles, Belgium). B-type natriuretic Peptide (BNP) was measured with a commercial analyzer (Triage BNP test, BIOSITE, California USA). Serum leptin and adiponectin levels were measured using human radioimmunoassay kits (KIPMR44, Biosource Europe SA, Belgium; and LINCO Research, USA, respectively). Serum human osteocalcin and insulin growth factor-1 (IGF-1) levels were measured using human immunoradiometric assay kits (KIP1381, Biosource Europe SA, Belgium; and IGF1-RIACT, CIS bio-international, France, respectively). Serum oxidative stress was measured with a commercially available method, that measures total hydroperoxides, expressed in conventional units (Carratelli units, UCarr, 1 UCarr corresponds to 0.8 mg/L H_2O_2; d-ROMs test; Diacron; Grosseto, Italy).[22,23]

EBC pH was measured after Argon deaeration, as previously described.[24] EBC TNF-α and 8-isoprostane were measured with commercial ELISA kits (Biosource Europe, Nivelles, Belgium; and Cayman Chemical, Ann Arbor, MI respectively).

Statistical analysis

Data are expressed as mean $\pm$ SD or as median (interquartile ranges) for normally distributed and skewed data,

respectively. Comparisons of biomarkers between COPD patients with and without emphysema were performed with Mann–Whitney U and unpaired Student's *t*-tests for skewed and normally distributed variables, respectively. Correlations were assessed using Spearman's and Pearson's correlation coefficients for skewed and normally distributed variables, respectively. *P* values <0.05 were considered statistically significant. Analysis was performed with SPSS 15 (SPSS, Chicago, IL).

Results

Subjects were divided into two groups according to their emphysema score in HRCT. Patients without significant emphysema ($n = 25$) had a HRCT emphysema score of 0 (0, 0.2), whereas patients with HRCT-confirmed emphysema ($n = 24$) had a score of 2.8 (1.12, 3.47).

Characteristics of study subjects according to the presence of emphysema in HRCT (Table 1)

There was no difference in age and smoking history between the two groups. However, patients with emphysema had lower FEV_1 and FEV_1/FVC ratio and worse diffusing capacity for carbon monoxide (DLco). Furthermore, TLC and RV did not differ between the two groups (despite a significant trend in the latter), but patients with emphysema had lower IC/TLC ratio (Fig. 1a) and higher RV/TLC ratio. There was a trend for lower exercise capacity, as expressed by the total distance walked in 6 min that did not reach statistical significance. Moreover, patients with emphysema had worse MRC dyspnea score (Fig. 1b), and higher BODE index (Fig. 1c). Additionally, patients with emphysema had lower BMI and FFMI compared to patients without significant emphysema (Fig. 2). Finally, patients with emphysema had a higher SGRQ total score, reflecting worse HRQoL (Fig. 3). This difference reflected mainly differences in the activity score and the impact in daily living, whereas no difference was observed in the symptoms score.

Differences of biomarkers according to the presence of emphysema in HRCT (Table 2)

Patients with emphysema had higher levels of systemic oxidative stress ($p = 0.005$) (Fig. 4a), lower circulating BNP levels ($p = 0.025$) (Fig. 4b), and higher plasma fibrinogen levels ($p = 0.006$) (Fig. 4c). A trend for higher TNF-α levels

Table 1 Characteristics of COPD patients according to the presence or absence of emphysema in HRCT.

	Non emphysema ($n = 25$)	Emphysema ($n = 24$)	*p* value
Age (years)	66.6 ± 9.6	65.4 ± 8.9	0.589
Pack-years	49.6 ± 15.7	60.6 ± 26.9	0.174
Current smokers	13/25	11/24	0.886
MMRC	2.0 (1, 2)	2.5 (2, 3)	**0.004**
PaO_2 (mmHg)	76.5 ± 9.1	71.6 ± 9.7	0.112
$PaCO_2$ (mmHg)	38.4 ± 4.3	39.5 ± 6.5	0.774
FEV_1 (% pred.)	61.1 ± 12.7	42.3 ± 17.3	**<0.001**
FVC (% pred.)	77.3 ± 12.4	62.9 ± 16.1	**0.003**
FEV_1/FVC	60.4 ± 7.8	52.6 ± 11.1	**0.016**
FRC (% pred.)	136.8 ± 21.6	156.8 ± 45.8	0.066
RV (% pred.)	143.1 ± 33.5	187.3 ± 87.3	0.063
IC(% pred.)	86.2 ± 15.3	67.3 ± 17.8	**0.001**
TLC(% pred.)	100.5 (95.9, 110.1)	103.0 (91.1, 130.2)	0.633
RV/TLC(% pred.)	131.7 ± 17.4	156.4 ± 35.7	**0.008**
IC/TLC(% pred.)	0.38 ± 0.09	0.27 ± 0.09	**0.001**
DLCO(mmol/min/kPa)	83.8 ± 13.6	51.0 ± 18.9	**<0.001**
DLCO/VA(mmol/min/kPa/L)	93.2 ± 15.4	62.9 ± 24.4	**<0.001**
SGRQ total	30.9 ± 12.9	47.0 ± 19.9	**0.005**
SGRQ symptoms	32.5 ± 18.1	41.3 ± 21.5	0.084
SGRQ activity	46.2 ± 20.9	63.7 ± 24.8	**0.021**
SGRQ impact	21.9 ± 13.4	39.4 ± 20.2	**0.002**
6MWD (m)	400.7 ± 54	336.0 ± 116.5	0.068
DSat (%)	1.0 (0.0, 2.0)	3.0 (0.75, 4.0)	0.108
DBorg	1.0 (1.0. 2.0)	1.0 (0.0, 3.0)	0.639
BODE index	2.0 (1.0, 2.0)	5.0 (2..0, 6.0)	**0.001**
BMI kg/m^2	27.3 ± 3.8	25.0 ± 3.5	**0.041**
FFMI kg/m^2	18.6 (17.7, 20.2)	16.4 (15.2, 19.6)	**0.041**

Values are reported as mean ± SD or median (interquartile ranges) for normally distributed and skewed data, respectively.
MMRC: modified Medical Research Council; FRC: functional residual capacity; RV: residual volume; TLC: Total lung capacity; IC: inspiratory capacity; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; SGRQ: Saint George respiratory questionnaire; BMI, body mass index; FFMI: Fat Free Mass index; 6MWD: 6 min walking distance; DSat: alteration in oxygen saturation after the 6MWT, DBorg: alteration in the level of dyspnea according to the Borg scale after the 6MWT, BODE: body mass index, airflow obstruction, dyspnea, exercise performance.

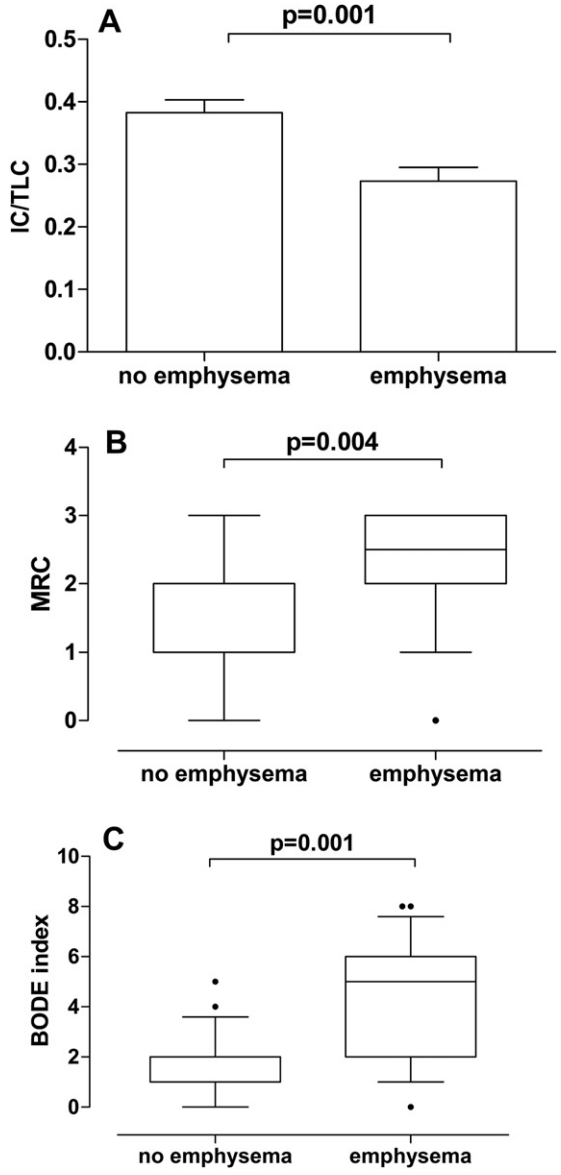

Figure 1 (A) Inspiratory capacity to total lung capacity ratio (IC/TLC), (B) Medical Research Council dyspnea scale, and (C) BODE index, in patients with COPD according to the presence or absence of emphysema on HRCT. Subjects with HRCT confirmed emphysema had higher BODE index, experienced worse dyspnea, and had lower IC/TLC ratio compared to subjects without HRCT confirmed emphysema. A: Data are presented as mean. B and C: Values are reported as median (interquartile ranges).

in patients with emphysema, however, did not reach statistical significance. No other significant differences were observed in the other biomarkers in blood or EBC that were examined between the two study groups.

Correlations between HRCT emphysema score and functional and clinical parameters in COPD patients

Significant correlations between HRCT emphysema score and functional and clinical parameters in COPD patients are shown in Table 3. The HRCT emphysema score presented

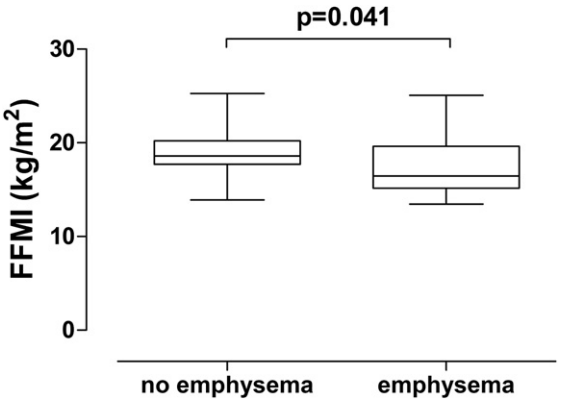

Figure 2 Fat free mass index (FFMI) in patients with COPD according to the presence or absence of emphysema on HRCT Subjects with HRCT confirmed emphysema have lower FFMI compared to subjects without HRCT confirmed emphysema. Values are reported as median (interquartile ranges).

significant correlations with virtually all functional parameters (dynamic and absolute lung volumes and diffusing capacity of the lung), and the measurements of body composition (BMI and FFMI). Furthermore, HRCT emphysema score presented significant correlations with HRQoL and exercise capacity in COPD patients. None of the biomarkers measured in blood samples or EBC presented significant correlations with the HRCT emphysema score.

Evaluation of significant differences according to disease severity

According to our observations, COPD patients with HRCT confirmed emphysema had more severe disease as assessed

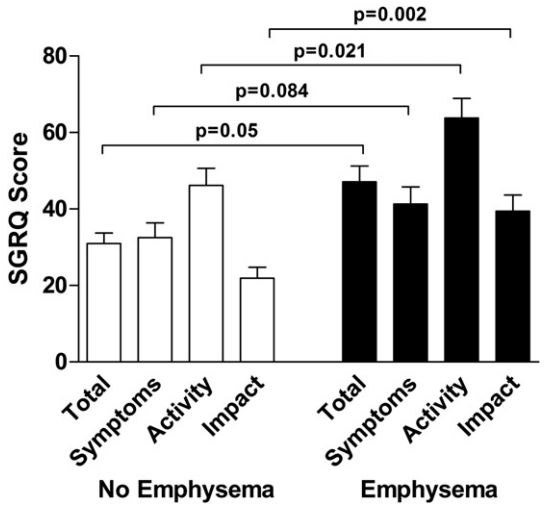

Figure 3 Saint George's Respiratory Questionnaire (SGRQ) total score, along with symptoms, activity and impact scores, in patients with COPD according to the presence or absence of emphysema on HRCT. Subjects with HRCT confirmed emphysema have higher total score, activity score and impact score in the SGRQ compared to subjects without HRCT confirmed emphysema. However, no significant different was observed in the symptoms score between the two study groups. Data are presented as means.

Table 2 Levels of biological markers in patients with COPD according to the presence or absence of emphysema on HRCT examination.

Marker	Non emphysema ($n = 25$)	Emphysema ($n = 24$)	p value
EBC pH	6.99 ± 0.38	6.87 ± 0.32	0.378
EBC 8-isoprostane (pg/ml)	3.50 (2.68, 6,58)	4.10 (3.07, 5.50)	0.693
EBC TNF-α (pg/ml)	21.00 (20.0, 22.79)	20.00 (20.00, 21.77)	0.209
Serum CRP (mg/dl)	0.20 (0.10, 0.35)	0.30 (0.10, 0.40)	0.675
Serum TNF-α(pg/ml)	37.03 (32.0, 43.42)	41.12 (34.83, 48.37)	0.074
Serum IL-6 (pg/dl)	8.70 (7.45, 11.50)	11.55 (7.52, 13.60)	0.177
Serum BNP (pg/ml)	31.40 (14.67, 69.82)	11.15 (6.85, 25.65)	**0.025**
Serum Oxidative Stress (UCARR)	235.00 (200.00, 281.00)	282.00(252.25, 344.75)	**0.005**
Plasma VEGF (pg/ml)	54.6 ± 17.0	60.6 ± 18.2	0.200
Plasma Fibrinogen (mg/dl)	406.00 (350.00, 461.00)	503.00 (430.50, 567.00)	**0.006**
Serum Adiponectin (ng/ml)	16.88 ± 6.23	18.44 ± 9.76	0.773
Serum Leptin (ng/ml)	4.49 ± 2.86	4.00 ± 2.77	0.529
Serum Leptin/Adiponectin	0.27(0.10, 0.44)	0.18 (0.10, 0.49)	0.812
Serum IGF-1 (ng/ml)	101.80 (87.45, 156.50)	119.50 (88.60, 188.4)	0.464
Serum Osteocalcin (ng/ml)	7.20 ± 4.28	5.68 ± 3.57	0.183

Values are reported as mean $\pm$ SD or median (interquartile ranges) for normally distributed and skewed data, respectively.
EBC: exhaled breath condensate, TNF-α: Tumour necrosis factor a, CRP: C-reactive protein, IL-6: interleukin 6, BNP: B-type natriuretic Peptide, VEGF: vascular endothelial growth factor, IGF-1: insulin-like growth factor.

by FEV_1. In order to ascertain whether the observed differences between the two study groups were due to the presence of emphysema itself or due to the presence of more severe disease, a multivariate linear regression model was performed using the clinical and laboratorial parameters that presented significant differences between the two groups as the outcome, and FEV_1 as a covariate. After adjustment for FEV_1, the two study groups still differed in all functional characteristics which have been previously reported as well as in serum oxidative stress ($p = 0.044$) and plasma fibrinogen ($p = 0.006$). However, patients with and without HRCT confirmed emphysema did not differ in BNP, BMI and FFMI levels ($p = 0.153$, $p = 0.252$, and $p = 0.095$, respectively).

Discussion

In the present study we have shown that COPD patients with HRCT-confirmed emphysema present worse pulmonary function, higher BODE index, worse dyspnea and health related quality of life, and lower BMI and FFMI, compared to COPD patients without emphysema. Patients with emphysema also had higher systemic oxidative stress and plasma fibrinogen levels and lower BNP levels compared to patients without emphysema. However, when adjusted for FEV_1, the two study groups did not differ in BNP levels, in BMI and in FFMI, whereas the rest of the differences remained, including the increased levels in systemic oxidative stress and plasma fibrinogen. This is the first study to our knowledge that addresses the issue of local and systemic biomarkers of inflammation in patients with HRCT-confirmed emphysema.

We confirm previous data reporting that COPD patients with HRCT-confirmed emphysema have worse pulmonary function.[11] In our study we have also shown that COPD patients with HRCT-confirmed emphysema have worse HRQoL, as expressed by the total score in SGRQ. Having in mind that the minimal clinically important difference in the SGRQ is a change of 4 units,[25] patients with emphysema experience greater limitations in everyday living since the difference between the two COPD phenotypes is almost 16 units. Unlike a recent study reporting that patients with emphysema differed in all parameters of SGRQ,[26] no significant difference was found in the symptoms score between the two groups of patients in our study. The above findings lead to the hypothesis that other factors apart from symptoms influence HRQoL in patients with emphysema. A factor that has been reported to be related to HRQoL in COPD patients is the frequency of exacerbations.[27] However, our study groups did not differ in exacerbation frequency as assessed by their medical records, although we have to admit that a recollection bias may exist at this point, since those data were retrospectively collected. On the other hand, it is well known that depression is a common comorbidity in patients with COPD, especially in patients with more severe disease,[28] and this may contribute to worse HRQoL in patients with emphysema.

Oxidative stress is a central feature in the pathogenesis of COPD.[29] Patients with emphysema presented no difference in EBC 8-isoprostane, a biomarker of lipid peroxidation that has been previously found elevated in COPD patients.[30] In contrast, systemic oxidative stress was significantly higher and serum TNF-α presented a trend to be elevated in patients with emphysema. A possible reason for the discrepancy between total systemic oxidative stress and other biomarkers of local and systemic inflammation in our study could be the fact that the method that we have used for the assessment of oxidative stress expresses the total oxidant burden in the body and is not specific for a solely marker of oxidative stress,[31] in contrast to the rest of the biomarkers that express specific aspects of inflammation. The fact that COPD patients with HRCT confirmed emphysema have higher levels of systemic oxidative stress, supports the hypothesis that the presence of emphysema is related to the action of free radicals outside the lung,[32] that is involved in the pathogeneses of muscle loss and

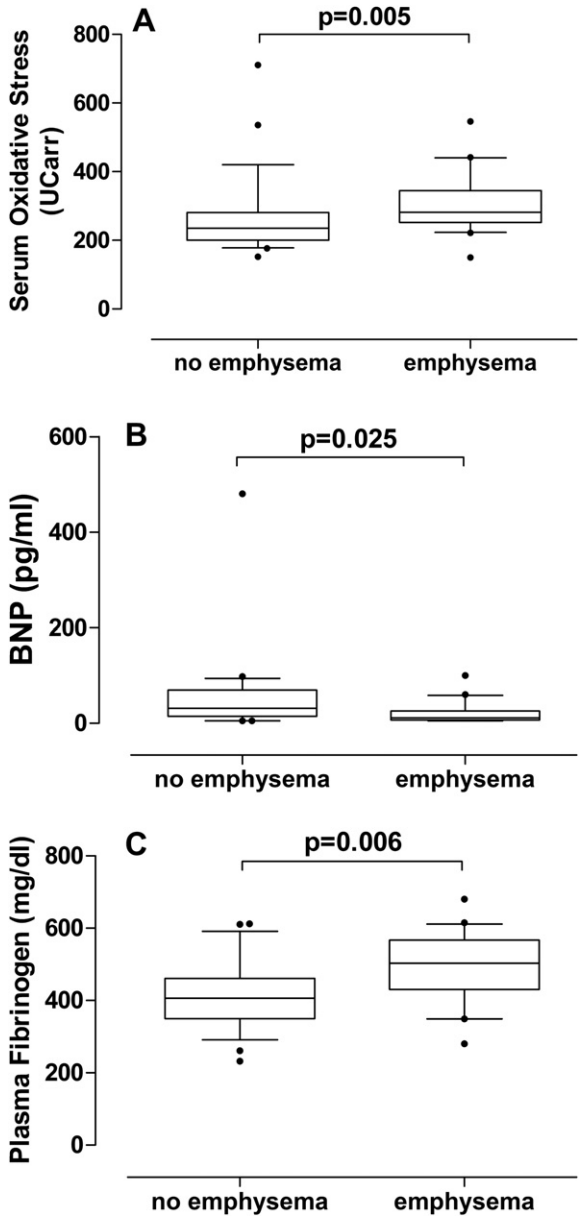

Figure 4 (A) Serum oxidative stress (B) B-type natriuretic peptide (BNP) and (C) plasma fibrinogen in patients with COPD according to the presence or absence of emphysema on HRCT. Subjects with HRCT confirmed emphysema had higher serum oxidative stress levels, lower circulating BNP levels and higher plasma fibrinogen concentrations, compared to subjects without HRCT confirmed emphysema Values are reported as median (interquartile ranges).

dysfunction in COPD patients,[32] while systemic inflammation causes nutritional abnormalities and weight loss.[33] Our data support the hypothesis that higher systemic levels of oxidative stress in COPD patients may contribute to the lower BMI and FFMI and the trend for impaired exercise capacity in those patients.

Cardiovascular comorbidities are common in COPD patients and represent a significant cause of mortality.[34] Elevated CRP and fibrinogen levels have been associated with greater cardiovascular mortality in COPD.[35,36] Serum

Table 3 Significant correlations between emphysema score in HRCT and functional and clinical parameters in COPD patients.

	r value	*p* value
MRC dyspnea scale	0.420	0.003
FRC	0.524	<0.001
RV	0.573	<0.001
TLC	0.493	0.001
RV/TLC	0.575	<0.001
FRC/TLC	0.324	0.03
IC	−0.500	0.001
IC/TLC	−0.662	<0.001
FEV_1	−0.640	<0.001
FVC	−0.478	<0.001
FEV_1/FVC	−0.506	<0.001
DLCO	−0.843	<0.001
SGRQ total	0.670	<0.001
SGRQ symptoms	0.350	0.019
SGRQ activity	0.595	<0.001
SGRQ impact	0.671	<0.001
BMI	−0.331	0.02
FFMI	−0.321	0.028
6MWD	− 0.471	0.001
BODE	0.683	<0.001

MMRC: modified Medical Research Council; FRC: functional residual capacity; RV: residual volume; TLC: Total lung capacity; IC: inspiratory capacity; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; SGRQ: Saint George respiratory questionnaire; BMI, body mass index; FFMI: Fat Free Mass index; 6MWD: 6 min walking distance; BODE: body mass index, airflow obstruction, dyspnea, exercise performance.

CRP levels did not differ between the two COPD phenotypes in our study, where patients with significant cardiovascular disease were meticulously excluded. However, the higher plasma fibrinogen levels in patients with emphysema could lead to the hypothesis that these patients might be at greater cardiovascular risk. In contrast, BNP levels were more elevated in patients without emphysema. BNP has been proposed as a non-invasive marker for the presence and severity of pulmonary hypertension in chronic lung disease.[37] A recent study has also shown that BNP levels were elevated in COPD patients with cor pulmonale.[38] Based on the above, we hypothesize that increased BNP levels in non-emphysematous COPD patients may represent higher risk for development of pulmonary hypertension and cor pulmonale, as in the ''blue-bloater'' phenotype. However, according to the fact that BNP levels did not differ in the two study groups when our data were corrected for FEV_1 one can hypothesize that the risk for the development of pulmonary hypertension in COPD patients is more closely associated with disease severity.

Nutritional abnormalities, such as weight loss and skeletal muscle loss and dysfunction, are common consequences of COPD.[33] In this study we have shown that patients with emphysema have lower BMI and FFMI compared to non emphysematous COPD patients. A recent study has shown that FFM decline in COPD patients is associated with worse lung function.[39] Furthermore, FFMI reflects better the skeletal muscle mass in patients with

COPD and has been recently shown to correlate to dyspnea, airway obstruction and exercise capacity.[40] Interestingly, though, neither BMI nor FFMI differed between our study groups when values were corrected for FEV_1. That observation also leads to the plausible hypothesis that both low BMI and low FFMI in our COPD patients with emphysema were associated to disease severity.

Leptin and adiponectin are adipose tissue hormones which have been found to be altered in COPD patients.[41,42] We found no difference in their levels between patients with and without emphysema, despite the significant difference in BMI and FFMI.[41,42] One possible explanation could be that those hormones may be also be involved in the systemic inflammation of COPD.[43] Insulin-like growth factor (IGF-1) is a peptide that normally supports muscle structure and function, that may be implicated in the development of muscle weakness in COPD.[44] COPD patients present decreased serum IGF-1 concentrations[45] and that those concentrations correlate to muscle strength.[44] The absence of significant difference in IGF-1 between COPD patients with and without emphysema, despite a difference in FFMI, supports the hypothesis that muscle dysfunction, and not only the amount of muscle mass, is important in COPD.

The incidence of osteopenia and osteoporosis is increased in COPD, being invariably present in patients with low BMI and FFMI.[46] Osteocalcin, a hormone produced by osteoblasts, is considered a biomarker of bone density,[47] being decreased in COPD patients receiving treatment with corticosteroids.[48,49] No significant difference was found in serum osteocalcin levels between patients with and without emphysema, despite the lower BMI and FFMI in the former. Possible differences in the use of corticosteroids in our patients may account for this discrepancy. Further studies in steroid naive patients with additional use of bone density measurements are needed in order to evaluate properly osteocalcin levels in the two phenotypes.

Our study presents several limitations. First, about half of the patients in each group were current smokers. However, comparisons in functional and clinical characteristics and biomarkers between current and ex-smokers did not reveal any significant differences (data not shown). Second, we excluded patients with significant cardiovascular comorbidities. However, we believe that the exclusion of those patients was important for the proper evaluation of biomarkers of systemic inflammation in the two phenotypes. Finally, we have used an observational method for the quantification of emphysema in HRCT, instead of special CT software. However, this method presents excellent correlation with densitometric quantitation[18] and can be performed in everyday clinical practice.

In conclusion, we have shown that COPD patients with HRCT-confirmed emphysema have more severe lung function impairment, lower BMI and FFMI and poorer HRQoL. Additionally, they present elevated systemic oxidative stress and plasma fibrinogen and lower BNP compared to COPD patients without emphysema. The fact that patients with emphysema had higher levels of systemic oxidative stress and plasma fibrinogen even after adjustment for disease severity, suggests that they may be more prone to the systemic consequences of COPD compared to patients without emphysema. Our study further supports that the optimal characterization of COPD phenotypes may lead to better prediction of prognosis and individualization of treatment in the future.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Supplementary information

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